REMARKS

The Office Action and the cited and applied reference have been carefully reviewed. No claim is allowed. Claims 93, 95 and 98-120 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 93, 95 and 98-119 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the amendments to claims 93 and 118 to recite that IGIF or IL-18 shows a single protein band with the activity of inducing interferon gamma at a position corresponding to 19,000±5,000 daltons on SDS polyacrylamide gel.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 93, 95 and 98-120 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al., *Infect. Immun.*, 61:64-70 (1993). This rejection is respectfully traversed.

The examiner relies on support for her position in the following statement of Okamura at page 3969:

> Thus, IGIF in the serum sample was proved to be the same IGIF as that found in the liver extract,

However, as applicants have repeatedly argued and cited, Okamura continues immediately after this statement to teach:

> …and it was considered to *be bound to another protein* or to exist *in an oligomeric form* (emphasis added)

This clearly teaches that the IGIF disclosed in Okamura differs from the factor disclosed in Nakamura at least in its form as well as in its

molecular weight. It is therefore clear to one of ordinary skill in the art that the IGIF disclosed in Okamura is not the same as the factor disclosed in Nakamura.

Furthermore, applicants (three of the present inventors are co-authors of the cited Okamura reference) clarify that the term "the same" in the above cited statement, "Thus, IGIF in the serum sample was proved to be the same IGIF as that found in the liver extract", means that the IGIF (molecular weight of 19 kDa) isolated by Okamura is the same as the IGIF (molecular weight of 75 kDa) contained in the factor (molecular weight of 75 kDa) disclosed in Nakamura. The following sentence in Okamura supports this position:

> The serum factor whose apparent molecular mass was previously found to be 75 kDa by gel filtration was shown to contain the same 18-19-kDa IGIF. (page 3966, right column, lines 6-8)

Taking these teachings into account, the IGIF disclosed in Okamura is not the same as the factor disclosed in Nakamura, but is contained in Nakamura's factor.

In applicants' previous arguments, applicants have argued that Nakamura did not purify the factor and isolate IGIF. The examiner, however, asserts that this argument is not persuasive because Nakamura also purified the same IGIF, which is evidenced by the statement, "it was further purified to apparent homogeneity by PAGE" (abstract), and by the detailed purification procedures (page 65, the last paragraph to the last paragraph of page 66). With due respect to the examiner, applicants believe that the examiner has misinterpreted the statement in the abstract of Nakamura. Nakamura states at page 68, right column, second paragraph:

> The purified substance was much smaller by SDS-PAGE (50 to 55 kDa) (Fig.2B) than by the molecular sieve technique (70 to 75 kDa) ... The molecular shape may also have influenced the result. Since the factor lost its activity in SDS-PAGE, we also failed to definitely establish that the band revealed by SDS-PAGE was the factor ... (emphasis added)

This statement clearly indicates that Nakamura failed in purifying the factor in order to isolate IGIF, because the factor lost its activity after SDS-PAGE.

Attached hereto is a revised Schematic Diagram, in which it is emphasized that Nakamura did not succeed in purifying and isolating a protein with IFN-γ inducing activity and a molecular weight of 19 kDa. While the examiner states that Nakamura's factor possesses the same biological activity as that of Okamura, applicants believe that this position is incorrect. As cited above, Nakamura clearly states that since *the factor lost its activity in SDS-PAGE, we also failed to definitely establish that the band revealed by SDS-PAGE was the factor*. It is apparent that Nakamura's factor did not possess its activity when purified from SDS-PAGE.

The examiner further states that one of ordinary skill in the art would have been motivated to make the antibodies to Nakamura's factor and reasonably would have expected success because Nakamura indicated the necessity of such monoclonal antibodies and because of the fact that the technology of making antibodies was well established and widely used in the art at the time the present invention was filed.

Applicants wish to point out that Nakamura did not succeed in obtaining monoclonal antibodies to Nakamura's factor at the time the Nakamura reference was published. Although Nakamura would have been

motivated to obtain monoclonal antibodies to Nakamura's factor and also would have been in the best position to have obtained monoclonal antibodies quickly, Nakamura in fact had difficulty and was unsuccessful in doing so. Even the cited Okamura reference, which was published almost two years after the Nakamura reference and which understood the motivation to produce monoclonal antibodies to Nakamura's factor, did not succeed in obtaining such monoclonal antibodies. This means that what was disclosed in Nakamura was not sufficient to allow one of ordinary skill in the art to obtain monoclonal antibodies, even if the technology for making monoclonal antibodies was well established in the art at the time the present invention was made. Accordingly, Nakamura cannot make obvious the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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